REXTORO Oral Testosterone Replacement Therapy (TRT)

Bone, Reproductive and Urologic Drugs Advisory Committee and DSRMAC

September 18, 2014

REXTORO Oral Testosterone Replacement Therapy (TRT)

Robert Dudley, PhD, DABT

President and CEO

Clarus Therapeutics, Inc.

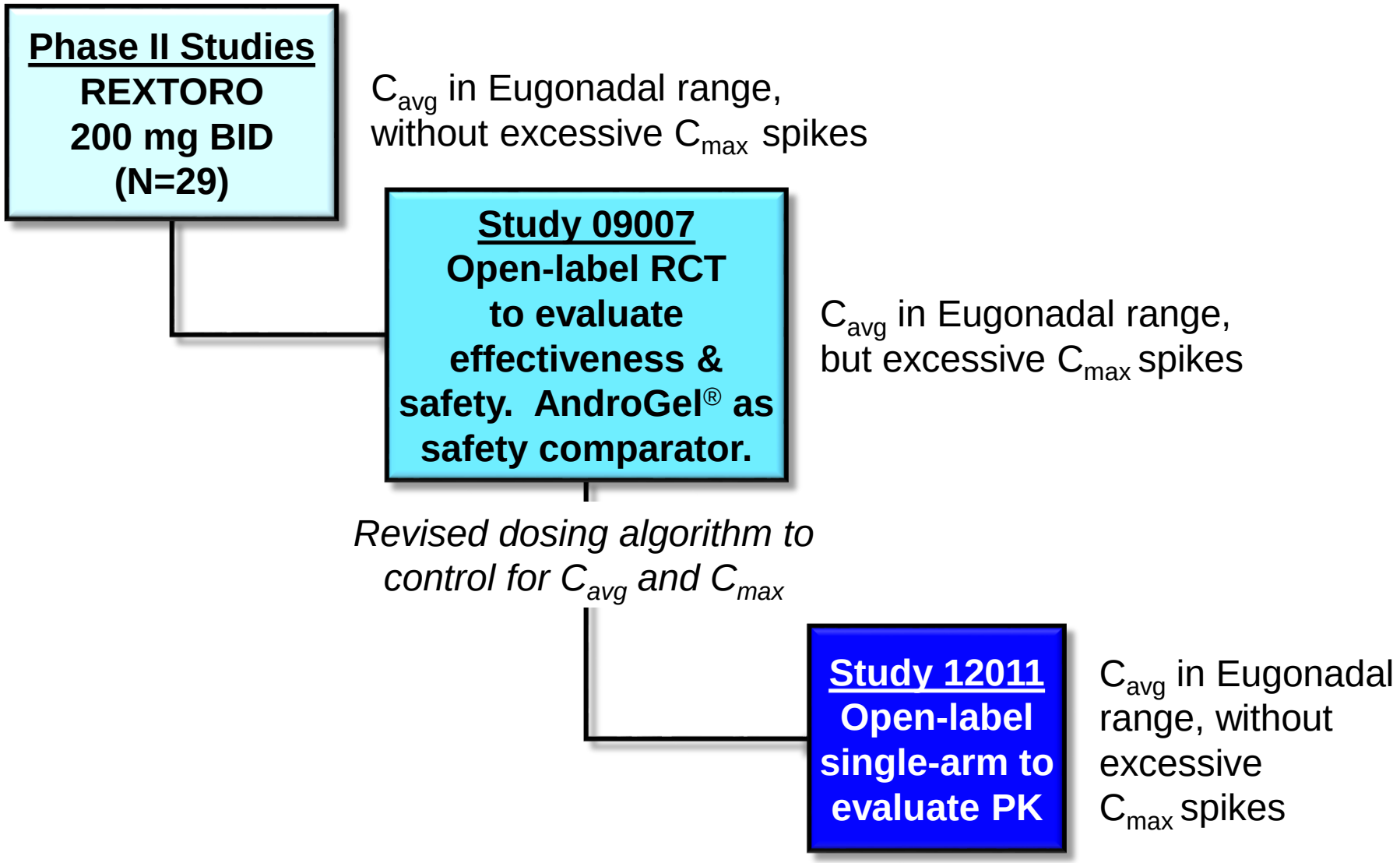
Proposed REXTORO Indication Same as Approved TRTs

- REXTORO is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
  - Primary hypogonadism (congenital or acquired)
  - Hypogonadotropic hypogonadism (congenital or acquired)

TRT Approved Based on a Single PK Study to Prove Effectiveness

- Effectiveness based on testosterone C_{avg}
- Serum testosterone C_{avg} established endpoint for TRTs
- Serum testosterone C_{avg} goals
  - ≥ 75% of efficacy population with C_{avg} of 300-1000 ng/dL
  - Lower bound of 95% CI ≥ 65%
- Frequency of high C_{max} values considered

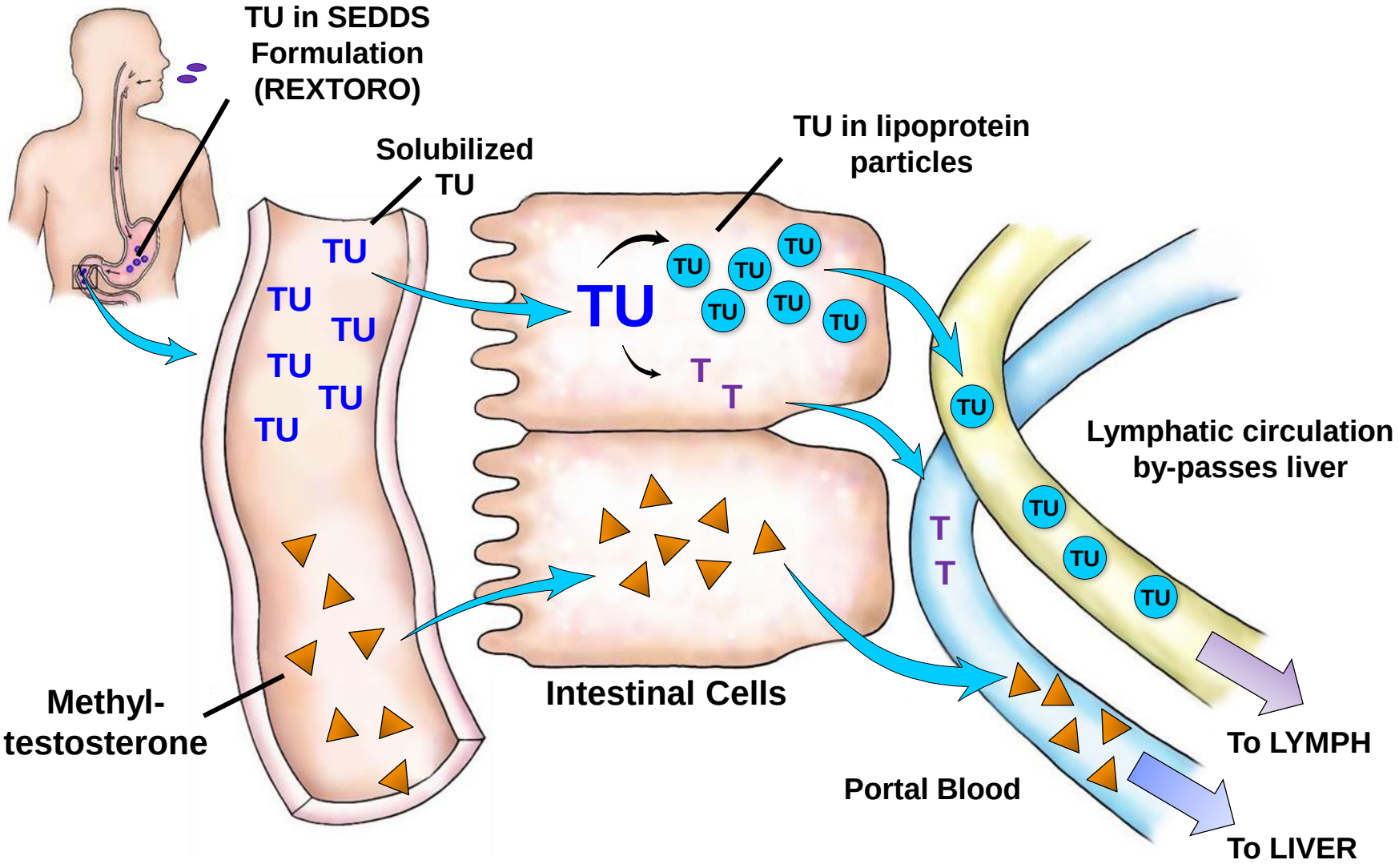
REXTORO NDA Supported by Phase III PK Studies 09007 and 12011



Study 12011 Dosing Algorithm Reduced C_{avg} for REXTORO

PK	Study 09007 Day 90 (N=146)	Study 12011 Day 114 (N=116)
Testosterone C_{avg} ng/dL (SD)	628 (± 343)	422 (± 171)

Absorption of REXTORO Primarily via Intestinal Lymphatic Pathway



Pharmacological Attributes of TU and DHTU Make Safety Risk Unlikely[1]

- TU and DHTU
  - Mainly in chylomicrons or bound to lipoproteins[2]
  - Do not easily enter or accumulate in tissues[3]
  - Metabolized by non-specific esterases and no accumulation[2,4]
  - No meaningful interaction with 87 binding targets used to assess safety risk[1]
  - Neither shows appreciable binding to androgen receptor[1]

1. Published literature and study reports used for ADME support of 505(b)(2) NDA; 2. Coert, *Acta Endocrinologica* (1977)
3. Horst & Erdmann *Horm Metab Res* (1980); 4. Baume, *Steroids* (2006).

Presentation Will Focus on Totality of Data that Support Approval

- REXTORO effectively restores circulating serum T levels
  - Consistent with regulatory precedent for approval
- Acceptable safety profile similar to approved TRTs
- Address FDA topics
  - Elevated TU and DHTU levels
    - Safety risk unlikely
  - Elevated DHT levels
    - Similar safety risk as other TRTs
  - Known CV and androgenic side effects
    - Similar safety profile and routine monitoring
  - Effect of missing data
    - Sensitivity analyses support effectiveness

Agenda

Unmet Need	**Glenn Cunningham, MD** Professor of Medicine and Molecular & Cellular Biology Baylor College of Medicine Houston, TX
Effectiveness	**Merrell Magelli, PharmD** Senior Director, Medical Affairs Clarus Therapeutics
Safety	**Theodore Danoff, MD, PhD** Senior Vice President, Clinical and Medical Affairs & CMO Clarus Therapeutics
Benefit-Risk	**Robert Dudley, PhD, DABT** President & CEO Clarus Therapeutics

Additional Responders

John Amory, MPH, MD	Professor of Medicine University of Washington School of Medicine
Kevin Billups, MD	Director, Men's Health & Vitality Associate Professor of Urology The Johns Hopkins Hospital
T. Hugh Jones, MD	Consultant Physician & Endocrinologist and Honorary Professor of Andrology, Barnsley Hospital NHS Foundation Trust
Jim Longstreth, PhD	PK consultant
Emile R. Mohler III, MD	Professor of Medicine and Director, Vascular Medicine, Perelman School of Medicine University of Pennsylvania
Abraham Morgentaler, MD, FACS	Associate Clinical Professor of Urology Harvard Medical School
Janet Wittes, PhD	President Statistics Collaborative, Inc.

Unmet Need

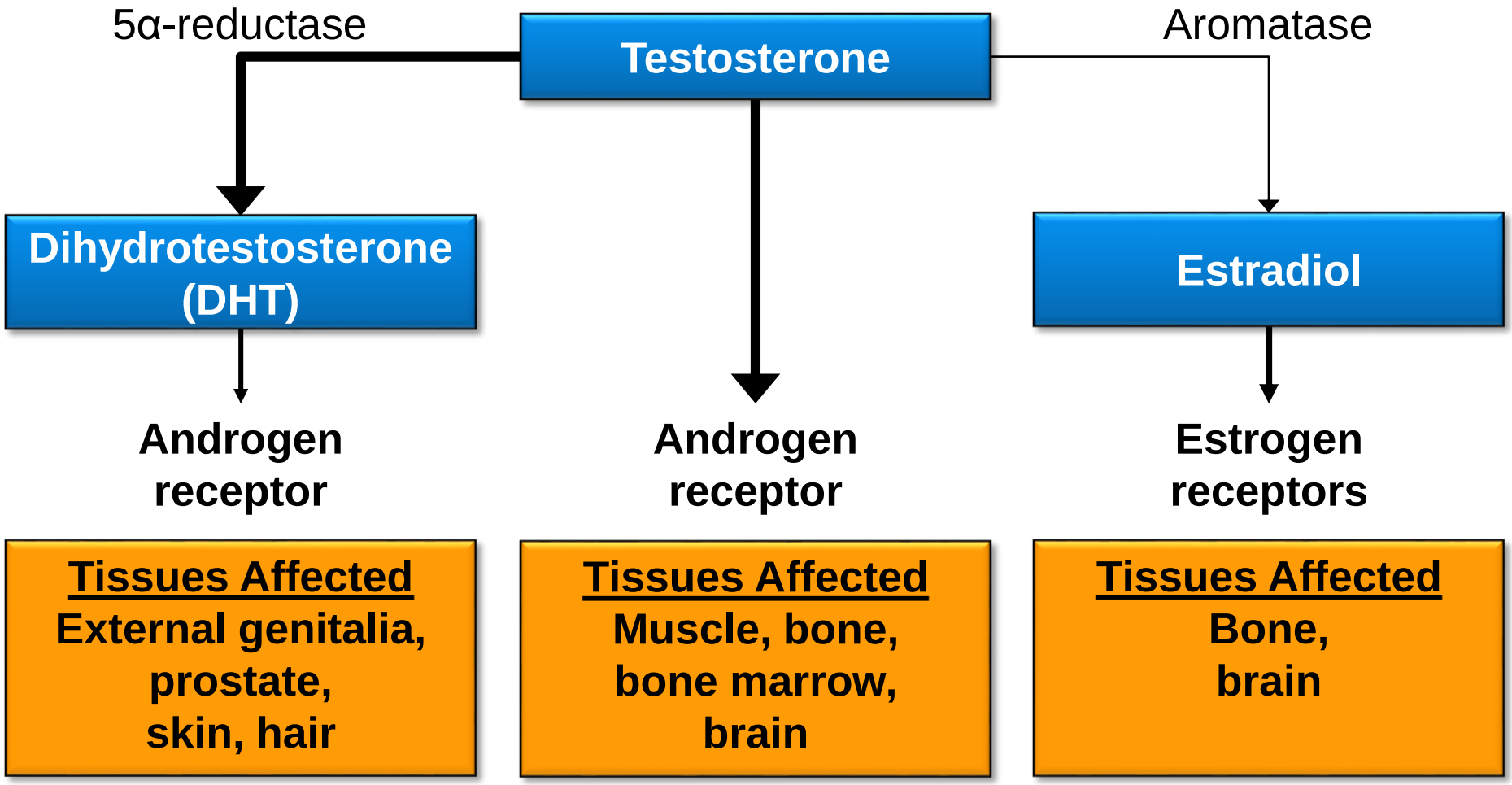
Glenn Cunningham, MD

Department of Endocrinology

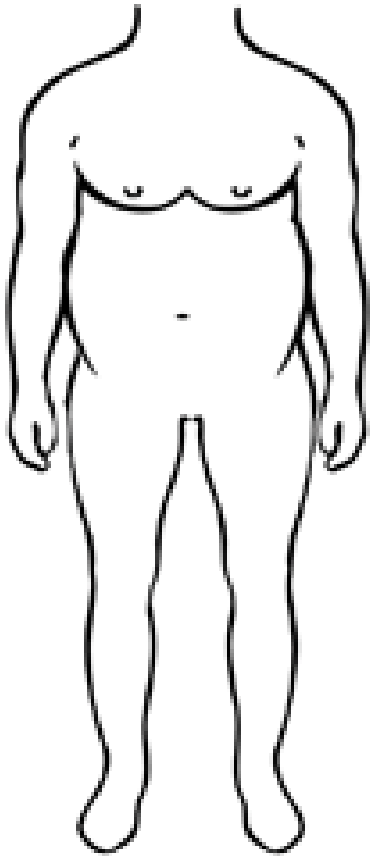
Professor of Medicine and Molecular & Cellular Biology

Baylor College of Medicine

Testosterone Metabolism



Hypogonadism Has Broad Spectrum of Clinical Manifestations



Hypogonadal Male

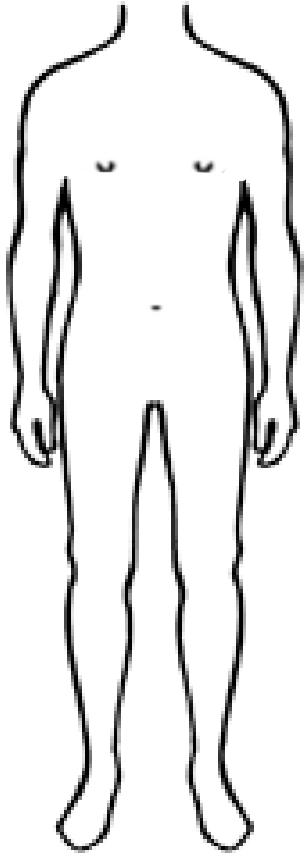
Brain and Sexuality
Libido and mood
Secondary sex characteristics

Muscle
Strength and volume

Fat
Adiposity / obesity

Bone
Bone mineral density

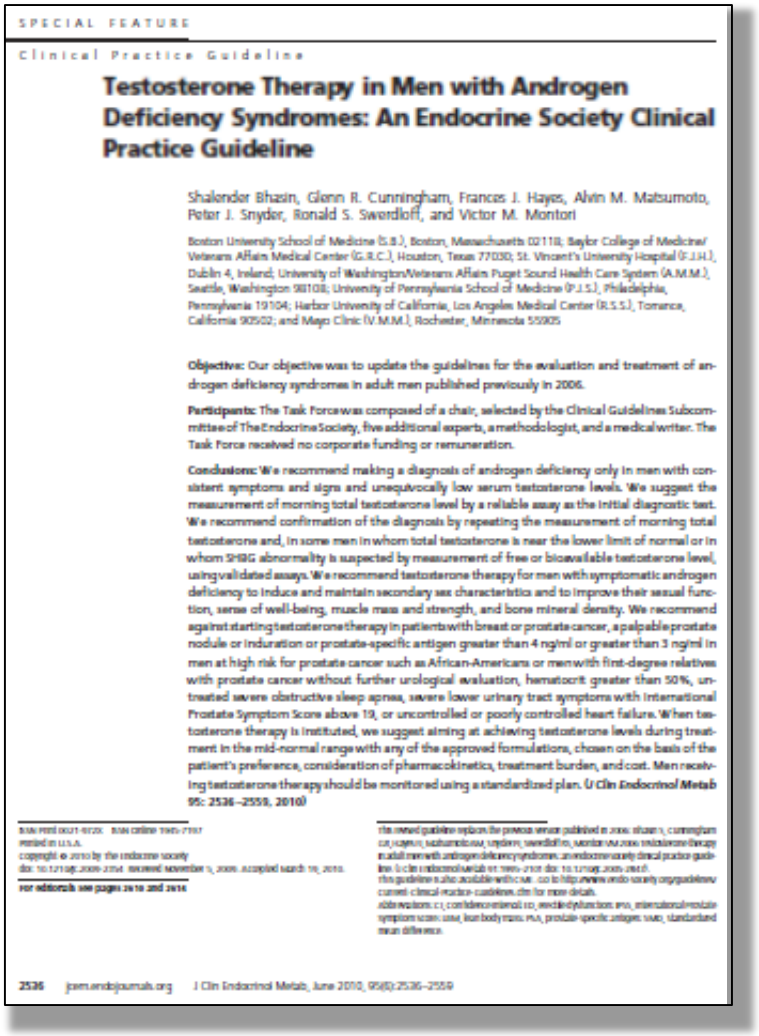
Blood
Erythropoiesis



Eugonadal Male

Endocrine Society Guideline: Men with Symptoms and Low Testosterone Levels

- "…improve sexual function, sense of well-being, muscle mass and strength, & bone mineral density."



SPECIAL FEATURE

Clinical Practice Guideline

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

Shalender Bhasin, Glenn R. Cunningham, Frances J. Hayes, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, and Victor M. Montori

Boston University School of Medicine (S.B.), Boston, Massachusetts 02118; Baylor College of Medicine/Veterans Affairs Medical Center (G.R.C.), Houston, Texas 77030; St. Vincent's University Hospital (F.J.H.), Dublin 4, Ireland; University of Washington/Veterans Affairs Puget Sound Health Care System (A.M.M.), Seattle, Washington 98108; University of Pennsylvania School of Medicine (P.J.S.), Philadelphia, Pennsylvania 19104; Harbor University of California, Los Angeles Medical Center (R.S.S.), Torrance, California 90502; and Mayo Clinic (V.M.M.), Rochester, Minnesota 55905

Objective: Our objective was to update the guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men published previously in 2006.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, a methodologist, and a medical writer. The Task Force received no corporate funding or remuneration.

Conclusions: We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and, in some men in whom total testosterone is near the lower limit of normal or in whom SHBG abnormality is suspected by measurement of free or bioavailable testosterone level, using validated assays. We recommend testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or prostate-specific antigen greater than 4 ng/ml or greater than 3 ng/ml in men at high risk for prostate cancer such as African-Americans or men with first-degree relatives with prostate cancer without further urological evaluation, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan. (*J Clin Endocrinol Metab* 95: 2536–2559, 2010)

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doi: 10.1210/jc.2009-2354 Received November 5, 2009. Accepted March 19, 2010.

For editorials see pages 2610 and 2614

This revised guideline replaces the previous version published in 2006: Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM 2006 Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 91:1995–2010 doi: 10.1210/jc.2005-2847. This guideline is also available online at http://www.endo-society.org/guidelines/current-clinical-practice-guidelines.cfm for more details.

Abbreviations: CI, confidence interval; ED, erectile dysfunction; IPSS, international prostate symptom score; LOE, level of evidence; PSA, prostate-specific antigen; SMD, standardized mean difference.

Bhasin, et al. J Clin Endo Metab (2010).

Six Delivery Modalities Approved in the United States

- Frequently prescribed (>95%)
  - Transdermal preparations
    - Gels, solutions or patches
  - Intramuscular (IM) injection
- Infrequently prescribed (<5%)
  - Buccal delivery system
  - Implantable pellets
  - Intranasal delivery
  - Oral formulation (methyltestosterone)

Transdermal Treatment Issues

- Daily applications and drying time
- Skin irritation in up to 15% of patients[1]
- Transference to women or children
  - Risk of virilization in women and children[2]
  - Risk of irreversible bone changes in children[2]
  - Black box warning[2]

1. Androderm® label; 2. Fortesta®, Testim®, Axiron®, AndroGel® and AndroGel® 1.62% labels

IM Injectable Issues

- Pulmonary Oil Micro Embolism (POME) and anaphylaxis risks[1,2]
- Short-Acting (e.g., Testosterone Enanthate)
  - Large peak-to-trough changes in T levels[3]
  - Can have prolonged high concentrations
- Long-Acting (e.g., AVEED™- TU)
  - Administered by a health care provider[1]
  - Black-box warning regarding POME and anaphylaxis[1]

1. AVEED™ label; 2. Delatestryl® label; 3. Bhasin, et al. J Clin Endo Metab (2010).

Alignment With Sept 17 BRUDAC Recommendations

- All TRTs should conform to forthcoming FDA label and communication requirements
- Enhance informed choice
- Appropriate patient selection
  - Low serum testosterone
  - Associated symptoms

Need for Safe and Effective Oral Option for Hypogonadism

- Hypogonadism is an endocrine disorder that requires chronic treatment; thus, an oral TRT may improve clinical management
- Adherence is low with current TRT therapies
  - Only 24% of currently treated patients are satisfied with their treatment options[1]
  - Oral TRT option is preferred[1]
    - May increase adherence

1. L.E.K. Study (2014).

REXTORO PK Effectiveness

Merrell Magelli, PharmD

Senior Director, Medical Affairs

Clarus Therapeutics

REXTORO Clinical Program

- Study 09007: supportive study for PK and safety
  - 12-month study
  - N=161, REXTORO: N=160, AndroGel
  - Primary effectiveness endpoint assessed at Day 90
- Study 12011: pivotal study for effectiveness and safety
  - 4-month study
  - N=144
  - Used final proposed dose titration algorithm
  - Primary effectiveness endpoint assessed at Day 114

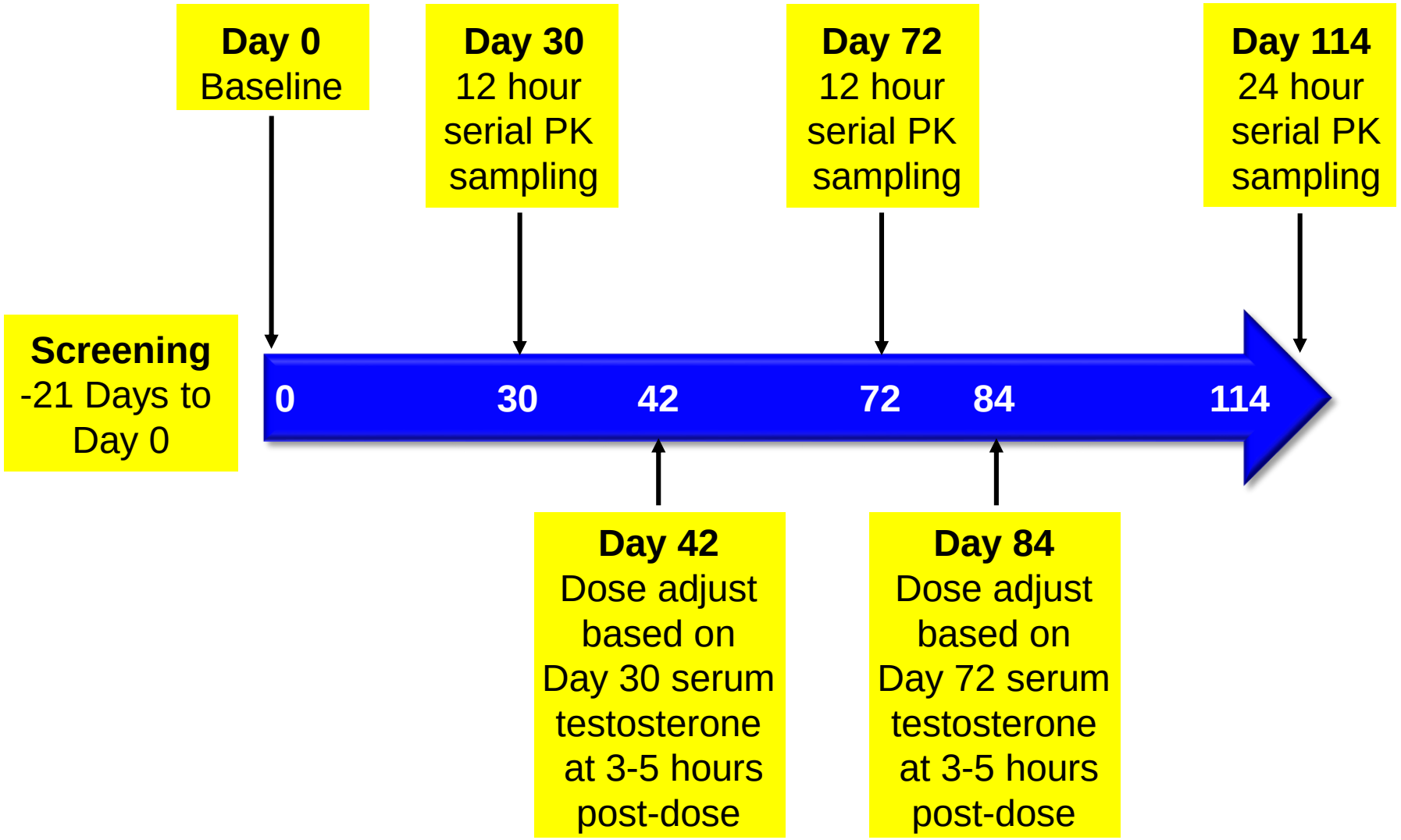
Phase III Inclusion Criteria

- Hypogonadal men
  - Total serum testosterone of ≤ 300 ng/dL
  - Age 18-75
- Naïve to androgen-replacement therapy or adequately washed out of prior androgen replacement therapies

Phase III Exclusion Criteria

- Significant uncontrolled intercurrent disease
  - CV, diabetes, severe sleep apnea
  - Liver or kidney dysfunction
- Hematocrit >48%
  - History of polycythemia
- Abnormal digital rectal exam, PSA >3.9 ng/mL, IPSS ≥ 19 or history of prostate cancer

12011 Study Design



Phase III Primary Endpoint: Restoration of Serum Testosterone to Eugonadal Range

- Percentages of patients whose testosterone C_{avg} based on 24-hour PK sampling in the eugonadal range (300-1000 ng/dL)
- Effectiveness demonstrated in efficacy population if
  - ≥ 75% of patients C_{avg} in normal range
  - Lower limit of 95% CI ≥ 65%

Phase III Secondary Endpoints Further Characterize Serum PK

- C_{max} based on 24-hour PK sampling was
  - ≤ 1500 ng/dL
  - >1800 ng/dL to 2500 ng/dL
  - >2500 ng/dL

Statistical Plan

- Studies powered to support regulatory primary PK endpoints
- Primary analysis conducted on efficacy population
- Two-sided test with a significance level of 0.05

Phase III Demographics

Characteristic	Study 09007 REXTORO (N=161)	Study 09007 AndroGel (N=160)	Study 12011 REXTORO (N=144)
Age (years)			
Mean (SD)	55.0 (11.06)	54.7 (11.18)	54.8 (10.60)
Race, N (%)			
Asian	0	5 (3.1)	13 (9.0)
Black	18 (11.2)	23 (14.4)	15 (10.4)
White	141 (87.6)	128 (80.0)	114 (79.2)
Other	2 (1.2)	4 (2.5)	2 (1.4)
BMI (kg/m^2)			
Mean (SD)	30.0 (3.90)	29.9 (3.97)	29.9 (3.92)

Phase III Baseline Characteristics

Characteristic	Study 09007 REXTORO (N=161)	Study 09007 AndroGel (N=160)	Study 12011 REXTORO (N=144)
Total testosterone at baseline (ng/dL)			
Mean (SD)	209 (108.4)	219 (103.7)	246 (94.8)
Baseline Clinical Characteristics, N (%)			
Pre-diabetic (glucose of 100-125 mg/dL)	62 (38.5)	56 (35.0)	45 (31.3)
Diabetes mellitus	31 (19.3)	32 (20.0)	25 (17.4)
Hypertensive	66 (41.0)	76 (47.5)	65 (45.1)
Statin, fibrate, omega-3 FA, or niacin use	67 (41.6)	73 (45.6)	54 (37.5)

Study 09007
PK Effectiveness Results

Study 09007: Patient Disposition

N (%) of Patients	Study 09007 REXTORO	Study 09007 AndroGel
ITT Population	162	163
Safety Population	161 (99.4%)	160 (98.2%)
Efficacy Population (PK at Day 90)	146 (90.1%)	149 (91.4%)
Patients who completed study	129 (79.6%)	133 (81.6%)
Patients who discontinued study	33 (20.4%)	30 (18.4%)
Adverse event	7 (4.3%)	4 (2.5%)
Lost to follow-up	7 (4.3%)	5 (3.1%)
Noncompliance with study drug	3 (1.9%)	0
Protocol violation	0	1 (0.6%)
Withdrawal of consent	12 (7.4%)	15 (9.2%)
Hematocrit > 54%	2 (1.2%)	0
Other	2 (1.2%)	5 (3.1%)

Study 09007 Achieved C_{avg} Primary Endpoint

% Within Range (Day 90)	REXTORO N=146	AndroGel N=149
C_{avg} < 300 ng/dL	7%	19%
C_{avg} 300-1000 ng/dL (95% CI)	84% (76%, 89%)	79% (72%, 85%)
C_{avg} >1000 ng/dL	10%	2%

Efficacy Population

Study 09007: Secondary Endpoints C_{max} Results

Study 09007 % Within Range (Day 90)	FDA Target	REXTORO N=146	AndroGel N=149
C_{max} ≤ 1500 ng/dL	≥ 85%	59%	93%
C_{max} >1800 to 2500 ng/dL	≤ 5%	13%	4%
C_{max} >2500 ng/dL	0 %	14%	1%

Efficacy Population

Pivotal Study 12011
PK Effectiveness Results

Study 12011: Patient Disposition

N (%) of Patients	Study 12011 REXTORO
ITT Population	148
Safety Population	144 (97.3%)
Efficacy Population (PK at Day 114)	116 (78.4%)
Patients who completed study	117 (81.3%)
Patients who discontinued study	27 (18.8%)
Adverse event	3 (2.1%)
Lost to follow-up	5 (3.5%)
Noncompliance with study drug	2 (1.4%)
Protocol violation	1 (0.7%)
Withdrawal of consent	8 (5.6%)
Hematocrit > 54%	3 (2.1%)
Other	5 (3.5%)

Study 12011 Dosing Algorithm Reduced Frequency of High C_{max} With Acceptable C_{avg}

	Study 12011	
Starting Dose	200 mg BID	
Down-Titration Guidelines		
Serum T Concentrations	>700 ng/dL	>1100 ng/dL in Study 09007
Decrements	50 mg BID	
Up-Titration Guidelines		
Serum T Concentrations	<250 ng/dL	
Increment	50 mg BID	
Single Sample Time	3-5 hours post dose	

Study 12011: Achieved Primary Endpoint

Study 12011 % Within Range (Day 114)	REXTORO N=116
C_{avg} < 300 ng/dL	23%
C_{avg} 300-1000 ng/dL	75.0%
(95% CI)	(66.1%, 82.6%)
C_{avg} >1000 ng/dL	2%

Efficacy Population

Study 12011: Secondary Endpoint C_{max} Results

Study 12011 % Within Range (Day 114)	FDA Target	REXTORO N=116
C_{max} ≤ 1500 ng/dL	≥ 85%	82%
C_{max} >1800 to 2500 ng/dL	≤ 5%	6%
C_{max} >2500 ng/dL	0 %	3% (N=4)

Efficacy Population

Study 12011: 4 Patients with Transient C_{max} > 2500 ng/dL on Day 114

Patient**	Day 30 C_{max}*	Day 72 C_{max}*	Day 114 C_{max} AM	Day 114 C_{max} PM
1	935	602	3340	1310
2	823	213	1190	2838
3	874	1040	2570	1360
4	499	835	1530	2840

*Post-AM dose
**514-003, 515-018, 517-015, 519-009

Study 12011 PK Analysis Included Sensitivity Assessments

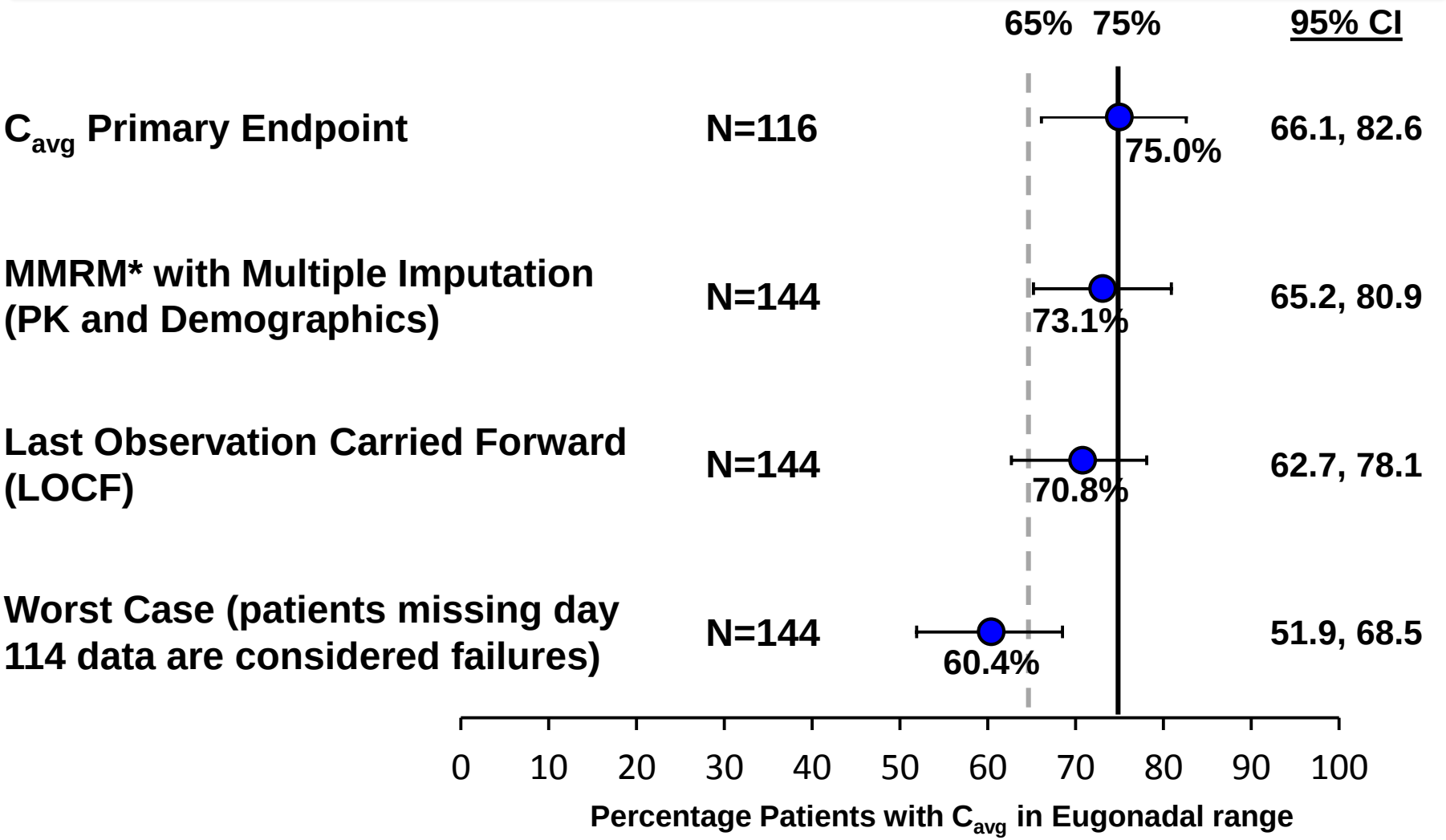
- Primary efficacy analysis (N = 116)
  - Patients with REXTORO PK at Day 114
- PK sensitivity analysis (N= 116 + 17 = 133)
  - 17 patients with PK at Day 30 and/or 72
- Safety population (N= 116 + 17 + 11 = 144)
  - 11 patients without REXTORO PK sample

Study 12011 PK Analyses Based on Available REXTORO PK Data

- Primary efficacy analysis (N=116)
  - Standard approach for PK approvals
  - Demonstrates dosing algorithm effect
- PK sensitivity analysis (N=133)*
  - 17 patients with REXTORO data
- Safety population (N=144)*
  - 11 patients with no REXTORO data
- Multiple imputation of Mixed Model Repeated Measure (MMRM) recommended*

***MMRM is recommended by the National Research Council (2010).**

Study 12011: Sensitivity Analyses to Address Missing Data (Safety Population)



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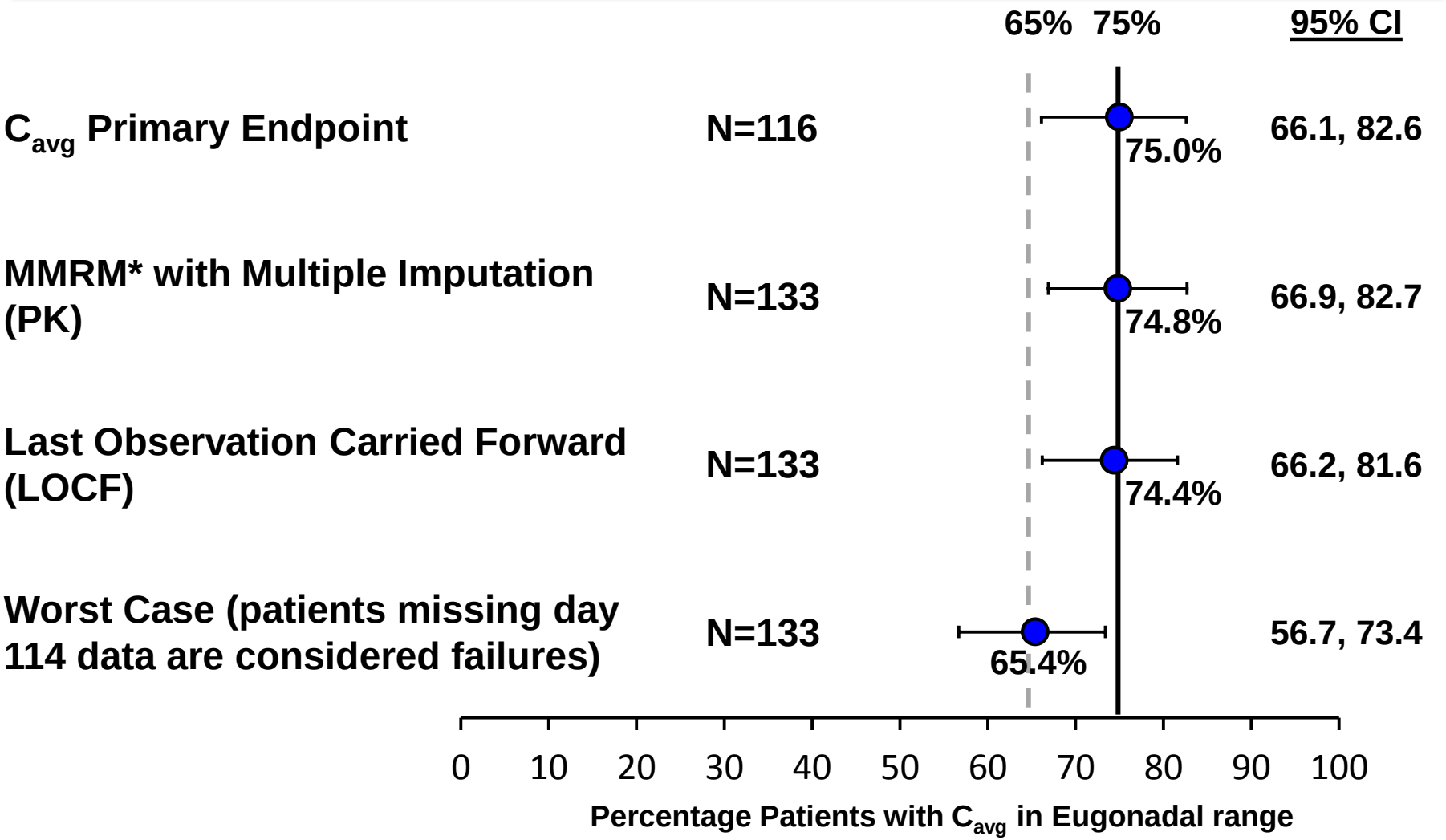
Study 12011: Sensitivity Analyses to Address Missing Data (PK Population)



*MMRM is recommended by the National Research Council (2010).

REXTORO Provides Effective T Replacement Based on PK Precedent

- Study 12011 achieved C_{avg} targets established for testosterone replacement approval
  - 75% of patients in eugonadal range
- Recommended dose titration algorithm restores testosterone to 300-1000 ng/dL while reducing C_{max} spikes

Safety

Theodore Danoff, MD, PhD

Chief Medical Officer

Senior Vice President, Clinical and Medical Affairs

Clarus Therapeutics

REXTORO Safety Profile Similar to Other TRTs

- Study 12011 may best represent safety profile
- AE differences often linked to TRT administration method
  - GI AEs with REXTORO
  - Avoids common administration-related AEs

Study 12011: Overall AE Rates

Event Code	Study 12011 REXTORO N=144
Any AE	48.6%
Any SAE	1.4%
AE Leading to Discontinuation	2.1%
Death	0

Study 12011: Common AEs (≥ 2%)

Preferred Term	Study 12011 REXTORO N=144 N (%)
Any AE	70 (48.6%)
Diarrhea	5 (3.5%)
Upper respiratory tract infection	5 (3.5%)
Hypertension	4 (2.8%)
Edema peripheral	4 (2.8%)
Nasopharyngitis	3 (2.1%)
Prostatomegaly	3 (2.1%)
Eructation	3 (2.1%)
Hemorrhoids	3 (2.1%)
Blood creatinine increased	3 (2.1%)
Blood glucose increased	3 (2.1%)
Hematocrit increased	3 (2.1%)

Study 12011: 2 Patients had SAEs

Preferred Term	Study 12011 REXTORO N=144 N (%)
Any SAE	2 (1.4%)
Cerebrovascular accident	1 (0.7%)
Worsening of COPD	1 (0.7%)

Study 12011: AEs Leading to Discontinuation

Preferred Term	Study 12011 REXTORO N=144 N (%)
AE Leading to Discontinuation (total)	3 (2.1%)
Palpitations	1 (0.7%)
Blood calcium increased	1 (0.7%)
Hypertension	1 (0.7%)

Study 12011: Cardiovascular AEs

System Organ Class Preferred Term, n (%) of patients	Study 12011 REXTORO N=144
Cardiac Disorders	2 (1.4%)
Atrial fibrillation	1 (0.7%)
Palpitations	1 (0.7%)
Nervous System Disorders (cardiovascular)	
Cerebrovascular accident	1 (0.7%)

Additional Safety Data from Studies 09007 and 12010

Elevated C_{avg} compared to Study 12011

Study 09007: Overall AE Profile

System Organ Class Preferred Term, % of patients	Study 09007 REXTORO (N=161)	 AndroGel (N=160)
Any AE	68.3%	62.5%
Any SAE	6.8%	3.8%
AE leading to discontinuation	5.0%	3.1%
Death	0	0

Study 09007: Cardiovascular AEs

System Organ Class Preferred Term, n (%) of patients	Study 09007 REXTORO (N=161)	 AndroGel (N=160)
Cardiac Disorders	7 (4.3%)	2 (1.3%)
Coronary artery disease	3 (1.9%)	1 (0.6%)
Cardiac failure congestive	2 (1.2%)	1 (0.6%)
Acute myocardial infarction	2 (1.2%)	0
Angina pectoris	2 (1.2%)	0
Palpitations	2 (1.2%)	0
Cardiomyopathy	1 (0.6%)	0
Coronary artery stenosis	1 (0.6%)	0
Left ventricular dysfunction	1 (0.6%)	0

Study 12010 Assessed Safety for Additional Year

- 12-month extension of Study 09007
- Open-label comparison of REXTORO to AndroGel
  - 178 patients received treatment
    - REXTORO (N=86)
    - AndroGel (N=92)

Study 12010 Long-term Extension: Similar AE Rate to AndroGel

Event Code	Study 12010 (>1 to ≤ 2 years) REXTORO (N=86)	AndroGel (N=92)
Any AE	54.7%	52.2%
Any SAE	7.0%	6.5%
AE leading to discontinuation	3.5%	6.5%
Death	0	0

Study 12010: Cardiovascular AEs

System Organ Class Preferred Term, n (%) of patients	Study 12010 (>1 to ≤ 2 years) REXTORO (N=86)	 AndroGel (N=92)
Cardiac disorders	3 (3.5%)	1 (1.1%)
Angina pectoris	1 (1.2%)	0
Atrial fibrillation	0	1 (1.1%)
Prinzmetal angina	1 (1.2%)	0
Tachycardia	1 (1.2%)	0
Nervous System Disorders (cardiovascular)		
Cerebrovascular accident	1 (1.2%)	1 (1.1%)

Common Testosterone-Related Adverse Events

Prostate

Hematocrit

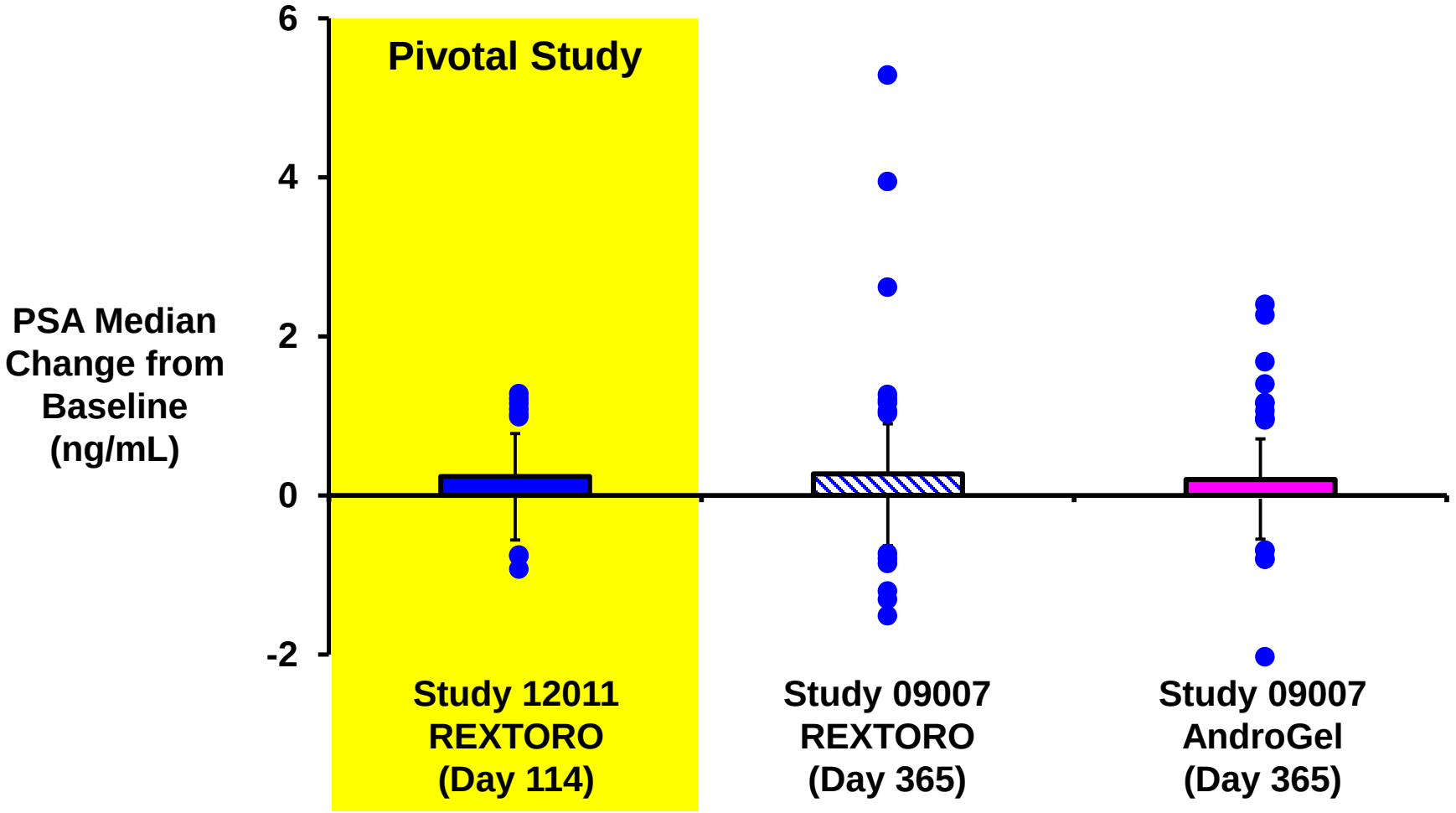
Lipids

No Meaningful Changes in Prostate Size or BPH Symptoms

- BPH symptoms evaluated by International Prostate Symptom Score (IPSS) and AEs
- Prostate size evaluated by transrectal ultrasound in Study 09007
- REXTORO similar to AndroGel in Study 09007
- Label will follow standard TRT warnings for PSA monitoring and worsening of BPH symptoms

PSA Levels are Known to Increase with TRTs

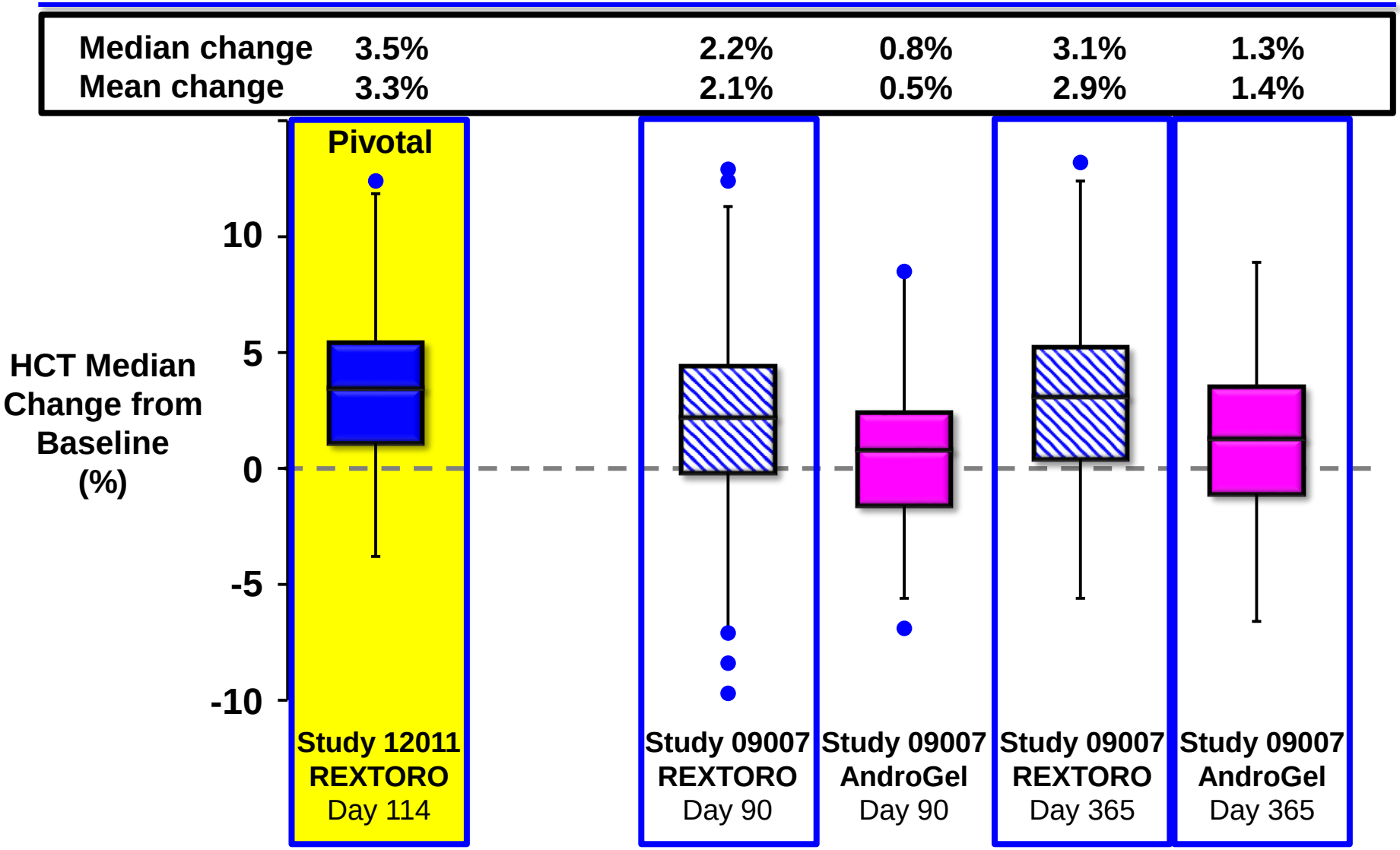
Median change (ng/mL)	0.1	0.2	0.1
Mean change (ng/mL)	0.3	0.3	0.2



18 Patients with Persistent PSA Increases; 15 Biopsied and 13 Were Negative

- Summary from 09007, 12011, and 12010
  - 18 had a persistent increase in PSA > 1.4 ng/mL
  - 15 underwent biopsy
    - 9 (2.4%) REXTORO and 6 (2.5%) AndroGel
- 2 patients on AndroGel were biopsy-positive for prostate cancer
  - 1 Gleason-7 (4 + 3)
  - 1 Gleason-9
- No prostate cancers in REXTORO arm

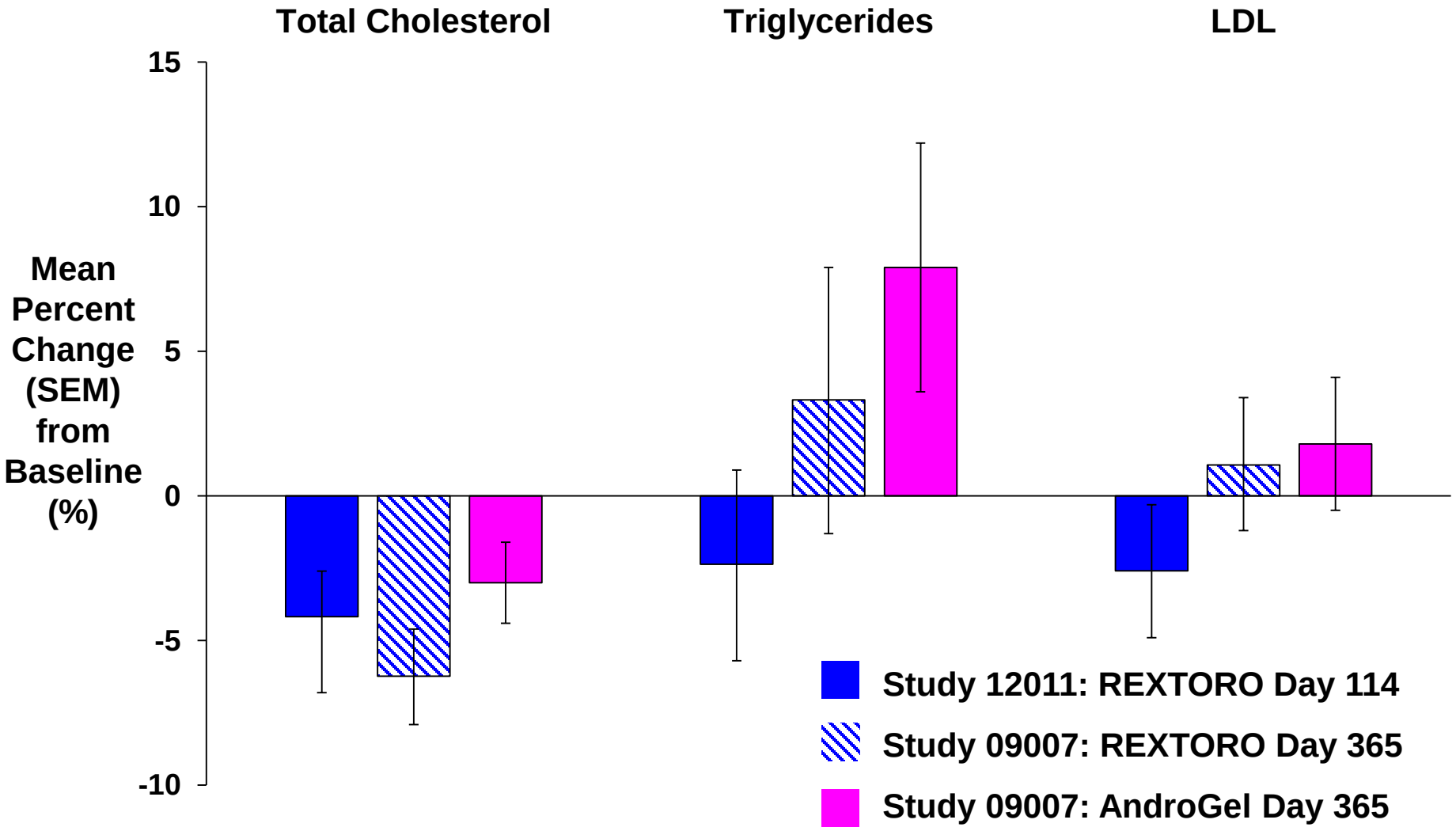
Hematocrit is Known to Increase with TRTs



Patients With Elevated Hematocrits Require Intervention

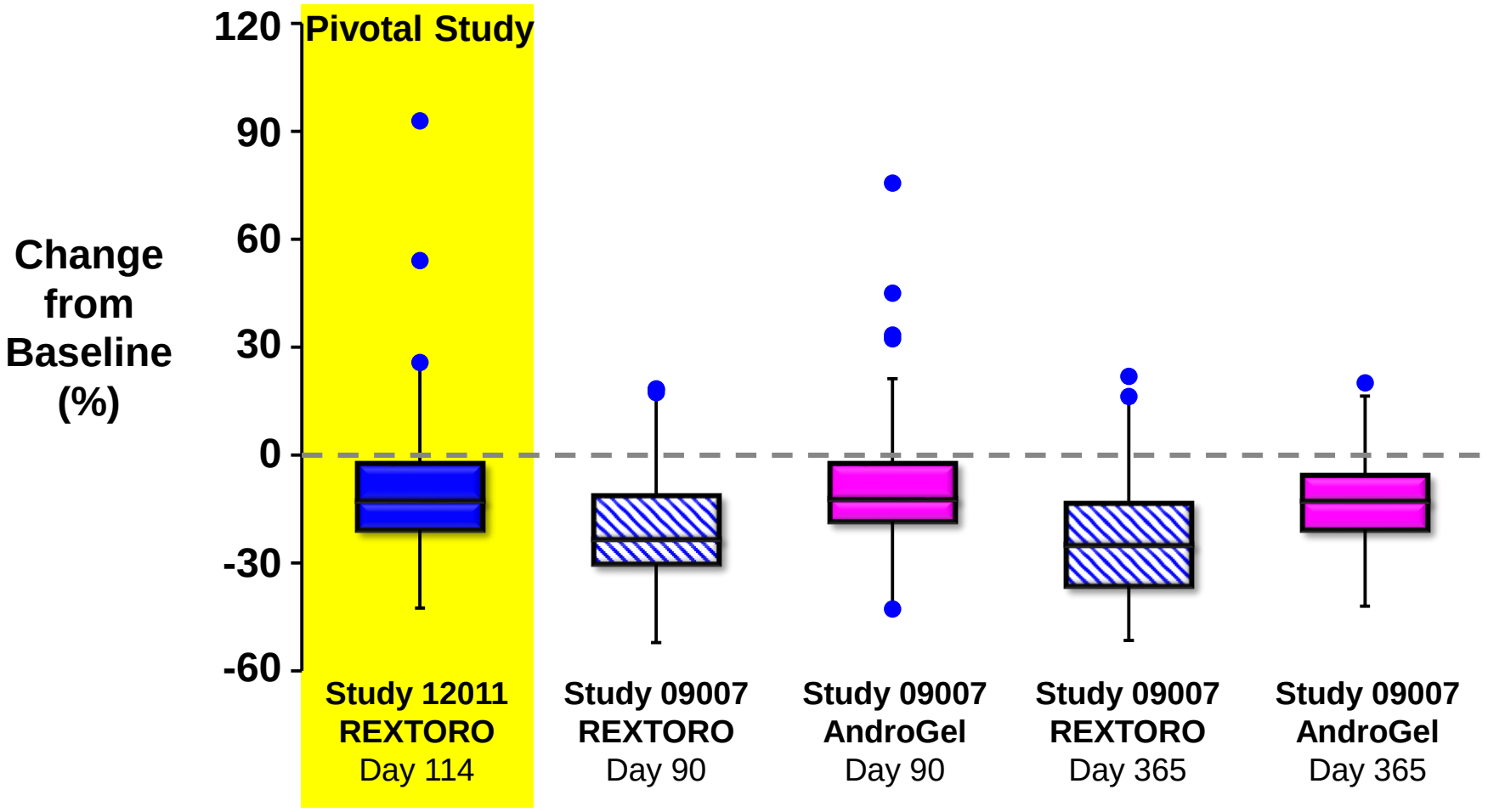
- Summary for Studies 09007 & 12010
  - Phlebotomy
    - REXTORO 7 (4%)
    - AndroGel 7 (4%)
  - Discontinued from study
    - REXTORO 4 (2.5%)
    - AndroGel 2 (1.3%)
- Summary for Study 12011
  - Discontinued 3 (2%)

REXTORO Minimal Effects on Total Cholesterol, Triglycerides and LDL



HDL is Known to Decrease with TRTs

Median change	-12.5%	-23.5%	-12.5%	-25.0%	-12.8%
Mean change	-9.9%	-20.7%	-9.2%	-21.6%	-12.3%



Area of Special Interest

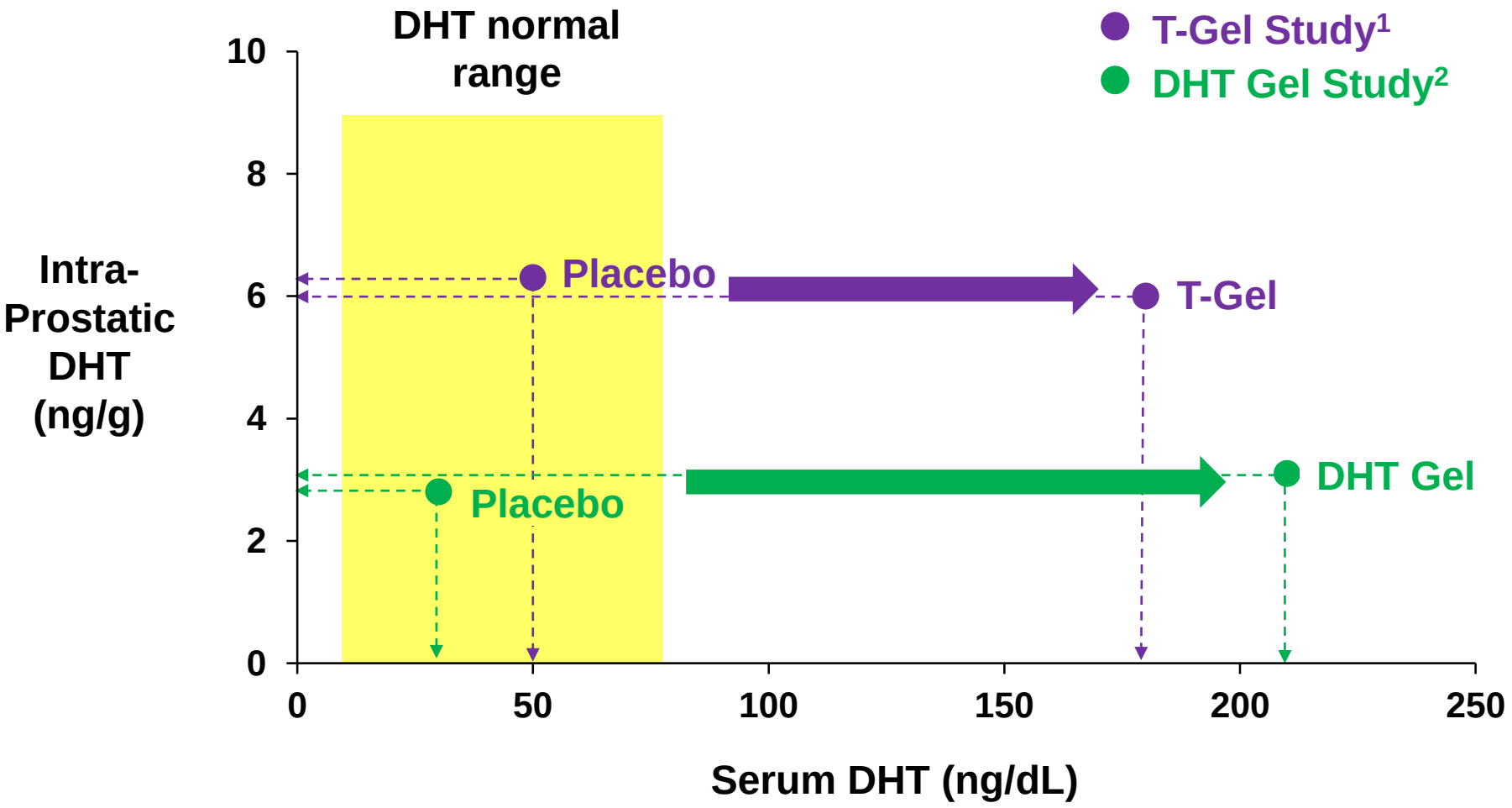
Dihydrotestosterone (DHT)

REXTORO Has Similar DHT Levels as Other TRTs

- Study 12011: C_{avg} DHT= 86.9 (±36.0) ng/dL
  - Normal range 13.7-76.9 ng/dL
- Elevated DHT levels reported for other recently approved TRTs
  - Axiron: C_{avg} DHT= 98.7 (±41.2) ng/dL[1]
- Clinical trials with DHT gel (DHT >200 ng/dL) did not identify increased AEs

1. Axiron Summary Basis for Approval

Intra-Prostatic DHT Levels Independent of Circulating DHT



1. Mostaghel, J Clin Endo Met (2012); 2. Page, J Clin Endo Met (2011).

Safety Conclusion

- REXTORO's safety profile similar to other TRTs
- Oral formulation avoids some serious administration related risks associated with gels and injections
- Study 12011 best represents what we should expect of REXTORO in clinical setting
  - Typical of pharmacological effects observed with TRT

REXTORO Benefit-Risk

Robert Dudley, PhD, DABT

Prescribing REXTORO Similar to Other TRTs and Requires Appropriate Monitoring

- Identification of appropriate patient population
  - Low serum testosterone and associated symptoms
- Monitoring of serum testosterone levels
  - Single sample
- Dose adjustment
  - Consistent with commonly prescribed gels
- Monitoring for physiologic changes and AEs

Benefits of Oral TRT Compared to Other Administration Methods

- At-home administration without gel application issues
  - Site reactions
  - Potential transference
  - Drying time
- No injection site pain or reaction
- Potential improved adherence

Recommended Dosing Algorithm Restored Mean C_{avg} to 422 ng/dL

- Achieve 300-1000 ng/dL while limiting C_{max} spikes
- Safety profile similar to approved TRTs when using revised dosing algorithm
- Evaluation at least 7 days after initiation and after each dose change
- Periodic monitoring

Education to Support REXTORO Dose Titration

- Educate health care providers (HCP) on dosing
- TRTs require dose adjustment
- Prescriber awareness of need for dose titration and dose titration algorithm will be evaluated at 6 and 12 months of approval
- Survey patients for understanding of the need to properly dose titrate
- Develop an understanding of knowledge gaps

Communicate Need for Ongoing Patient Monitoring

- Dear HCP Letter distributed within 60 days of approval and again around 12 months
  - Targeted to likely prescribers of REXTORO
- Emphasize diagnosis based on Endocrine Society Guidelines
- Emphasize need for periodic blood and safety monitoring

Hypogonadism Can be a Serious Medical Condition Requiring Long-term Therapy

- Symptomatic patients with serum testosterone levels consistently < 300 ng/dL face physical and emotional issues
- REXTORO is effective TRT, with a safety profile consistent with testosterone physiology
  - Supported by risk management plan
- Oral therapy can address limitations of current TRT therapies
  - May enhance TRT adherence

REXTORO Oral Testosterone Replacement Therapy

Bone, Reproductive and Urologic Drugs Advisory Committee and DSRMAC

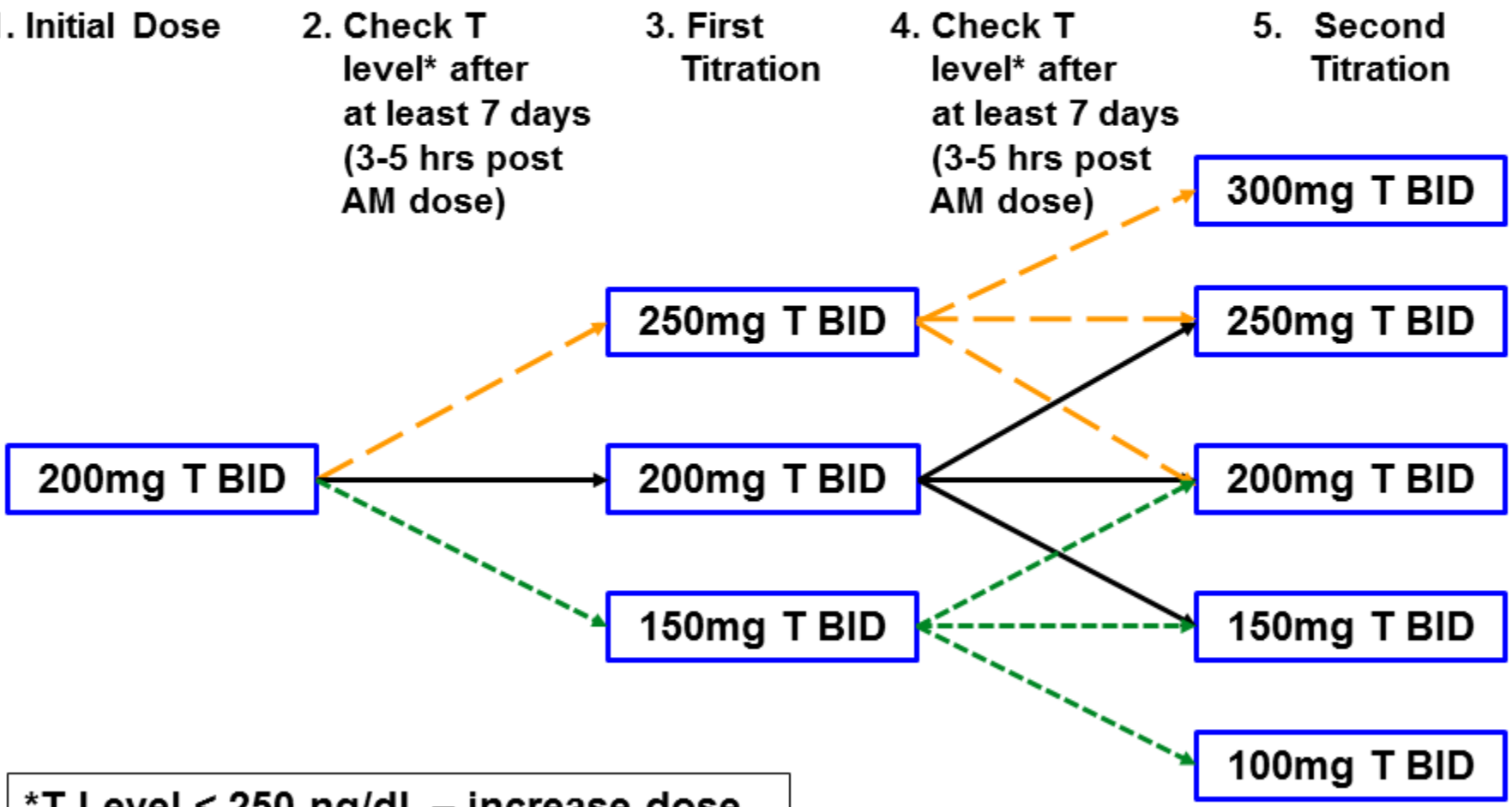
September 18, 2014

Backup Slides Shown

Bone, Reproductive and Urologic Drugs Advisory Committee and DSRMAC

September 18, 2014

Titration Steps



*T Level < 250 ng/dL – increase dose
*T Level > 700 ng/dL – decrease dose

Dosing Algorithms

	Study 09007	Study 12011
Starting Dose	200 mg BID	200 mg BID
Down-Titration Guidelines		
Serum T Concentrations	>1100 ng/dL	>700 ng/dL
Decrements	Initial: 100 mg BID Subsequent: 50 mg BID	50 mg BID
Up-Titration Guidelines		
Serum T Concentrations	<250 ng/dL	<250 ng/dL
Increment	Initial: 100 mg BID Subsequent: 50 mg BID	50 mg BID
Single Sample Time	4-6 hours post dose	3-5 hours post dose

Study 12011: Dose Titrations

Dose	Baseline	First Titration (Day 42) based on Day 30 C3-5 hour sample	Second Titration (Day 84) based on Day 72 C3-5 hour sample
Number at start of period (%)	144	130	118
300 BID	NA	NA	0 (0.0%)
250 BID	NA	2 (1.5%)	4 (3.4%)
200 BID	144 (100%)	62 (47.7%)	28 (23.7%)
150 BID	NA	66 (50.8%)	58 (49.2%)
100 BID	NA	NA	28 (23.7%)

NA-Dose not available at this time point due to incremental adjustments.

Study 12011: Discontinuations Due To Increase in HCT* (1-2)

Patient #	DC Date/ Study Day	Hct @ ET	Hct @ Scr or BL	Previous TRT	Cavg	Cmax	IP Dose	AEs
507-010	Day 11	49.00	49.00	NA	NA	NA	200mg BID	None
515-009	Day 101	56.40	46.30	Testopel	462 Day 72	793 Day 72	150mg BID	polycythemia
526-039	Day 98	54.90	46.50	NA	759 Day 72	1340 Day 72	200mg BID	None

* All Patients Were TU Patients

Study 12011: Early Withdrawal "AE"

Patient	Reason for Early Withdrawal "AE"
510-007	Worsening of hypertension
515-017	Heart palpitations
519-001	Abnormal lab serum calcium = 10.4

Study 12011: Examples of Meal Choices

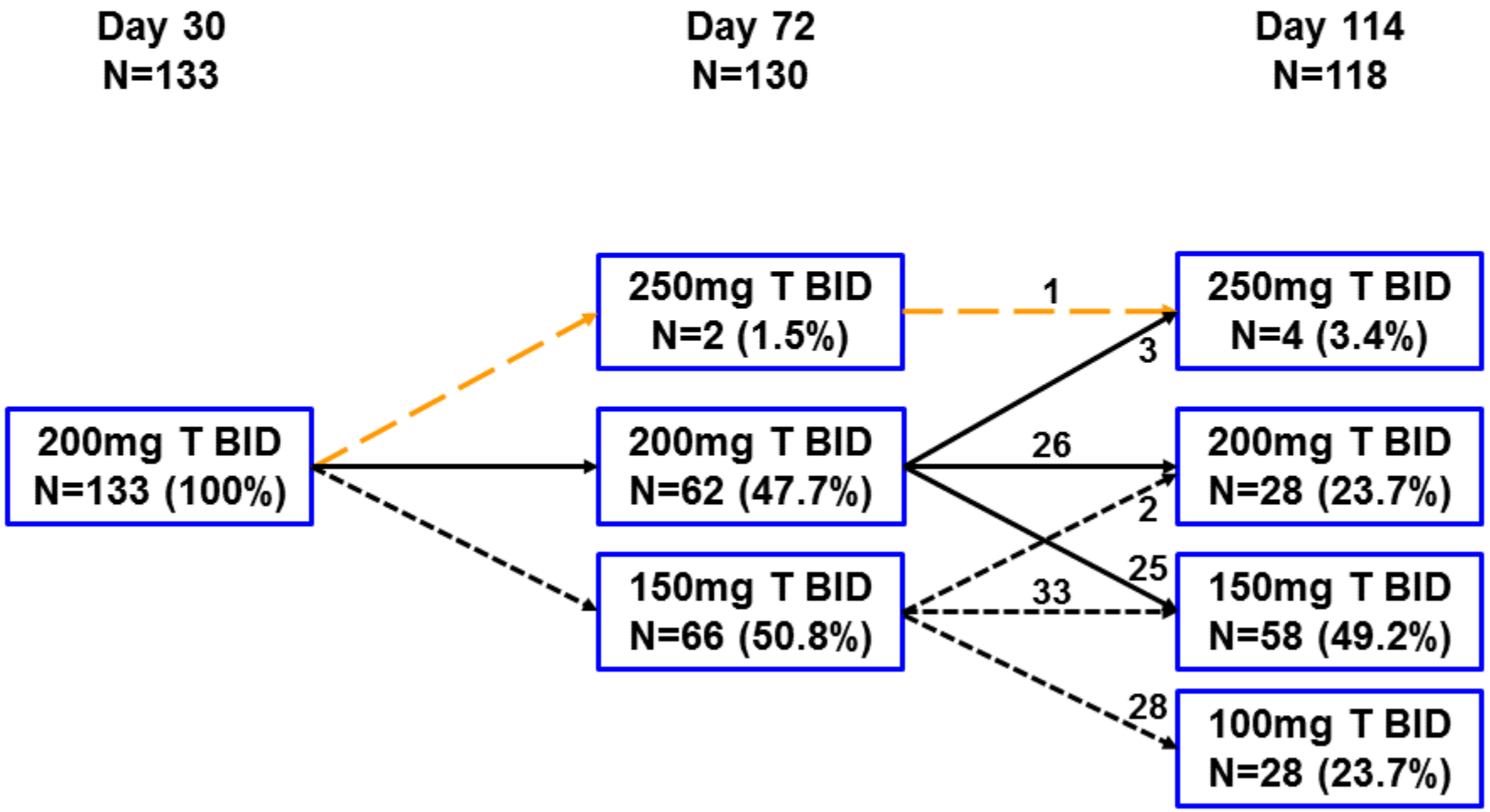
Breakfast		Dinner	
Oranges, raw, navel	Egg, whole, cooked, hard-boiled	Macaroni	Fish sticks (halibut or cod)
Chobani Greek nonfat honey yogurt	Bananas, raw	Sauce (marinara)	Sweet potato, baked with skin
Aunt Jemima Pancakes and Sausage	Milk	Meatballs	Green beans
Butter	Butter	Tossed salad and dressing	Croissant and butter
	Quaker oatmeal, maple and brown sugar	Rolls	Lipton Brisk Tea
			Chobani Greek nonfat honey yogurt

Study 12011 Serum T C_{avg} <300 ng/dL and C_{3-5} <250 ng/dL on Day 114

Serum T C_{avg}	Serum T C_{3-5}
184 ng/dL	236 ng/dL
283 ng/dL	232 ng/dL
252 ng/dL	169 ng/dL
223 ng/dL	204 ng/dL

(N=26 patients Cavg <300 ng/dL on Day 114)

Study 12011: Summary of Titration Steps



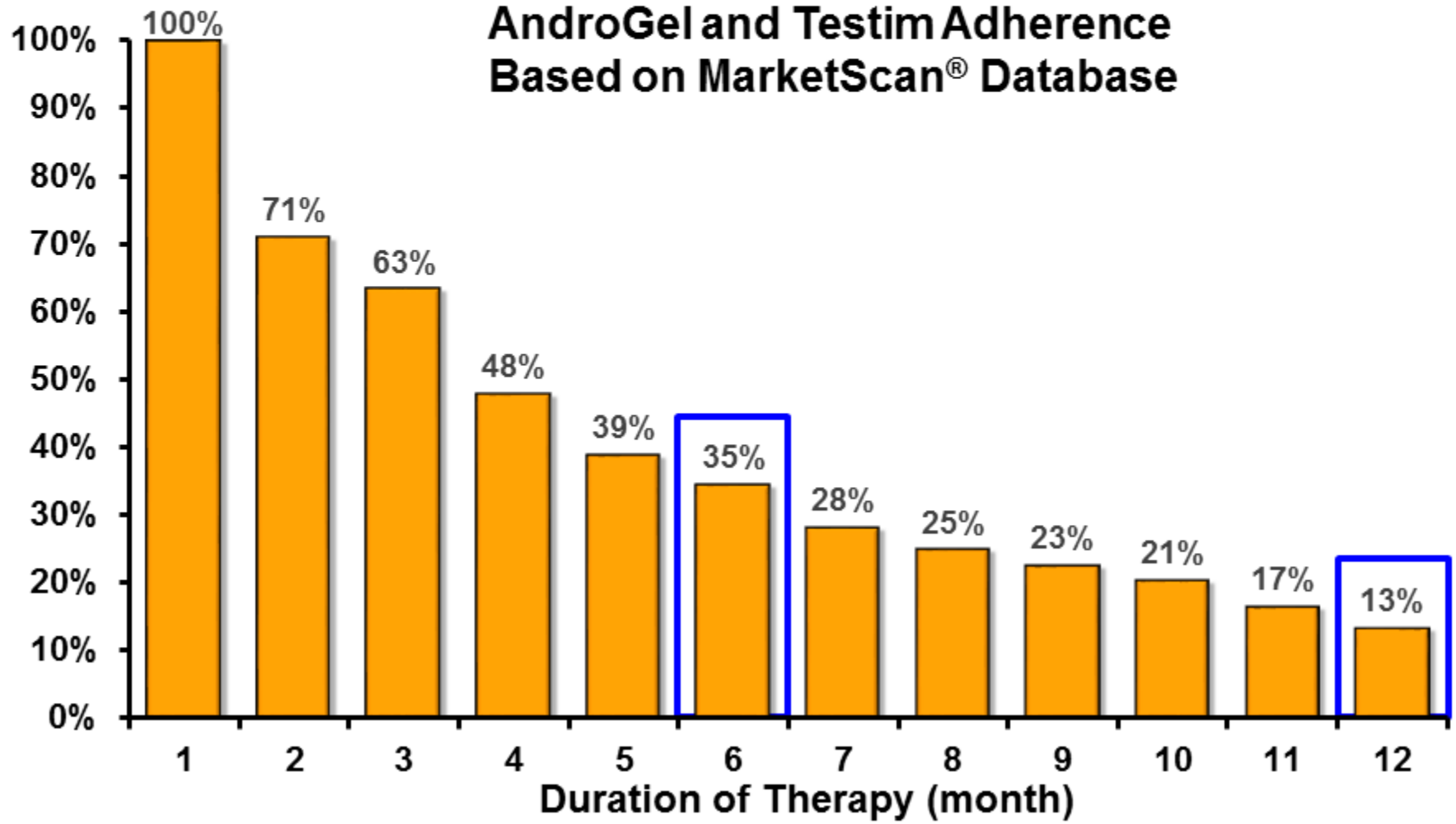
Patients Preference for Oral Medication

- Fallowfield L, etal, 2005
  - 63% of patients preferred tablets for administration of endocrine treatments
- Metaxas, C etal, 2013
  - Majority of patients preferred oral therapy to other available treatments – a Pubmed and EMASE search
- Liu G, etal 1997
  - 89% of patients preferred oral treatment to parenteral chemotherapy

Adherence to Oral Medication

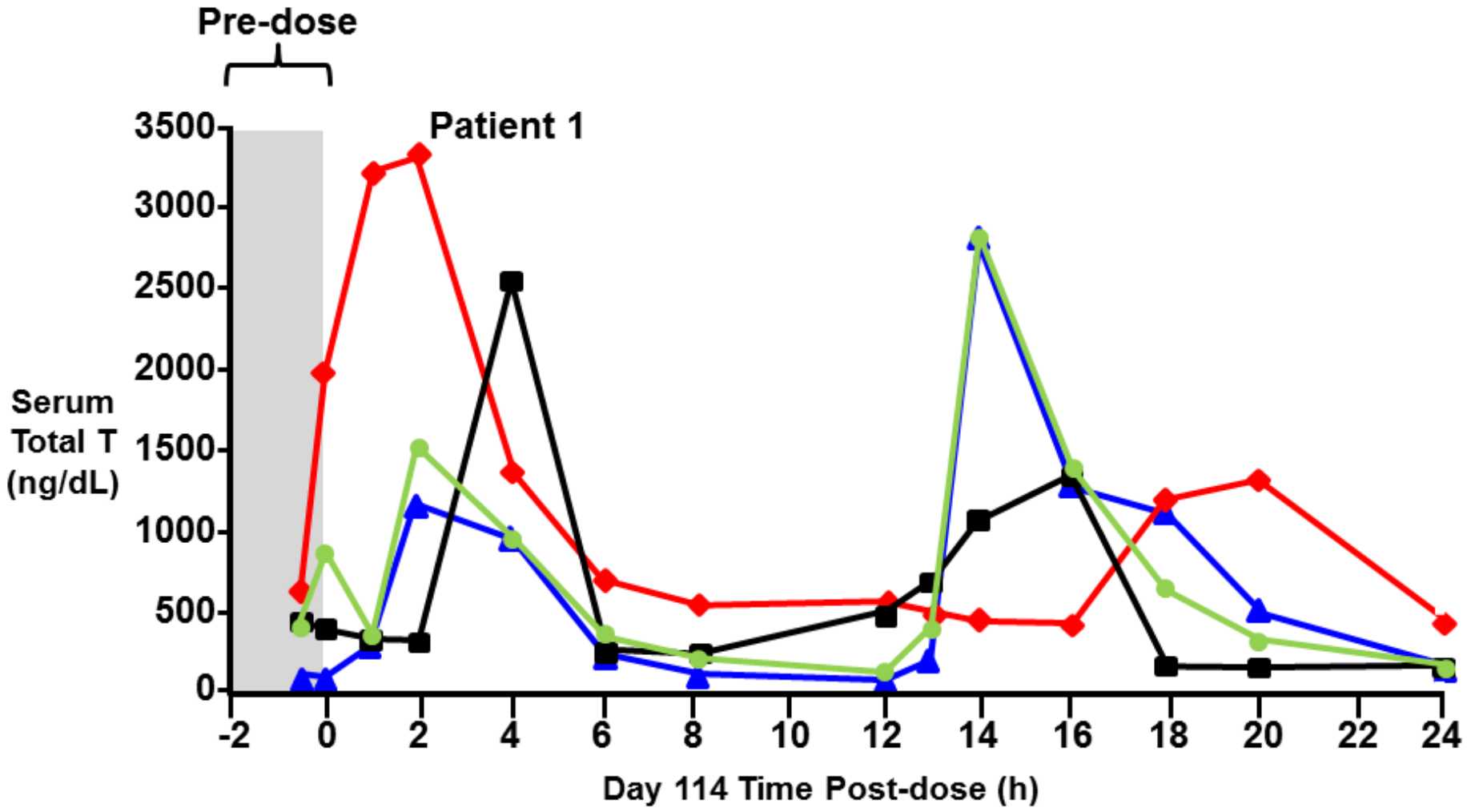
- Zaghloul SS, etal. Objective assessment of compliance with treatments in acne. Br J Dermatol. 2005;152(5):1015-1021.
  - Medication adherence rate of oral (isotretinoin) was 74.1% higher when compared with topical medication
- Liu G, et al. Patient preferences for oral versus intravenous palliative chemotherapy. JCO. 1997;15(1):110-115
  - Patients with incurable cancer have a clear preference for oral CT vs. IV Chemotherapy

Rapid Drop Off In Transdermal TRT Adherence



Schoenfeld J Sex Med, 2013

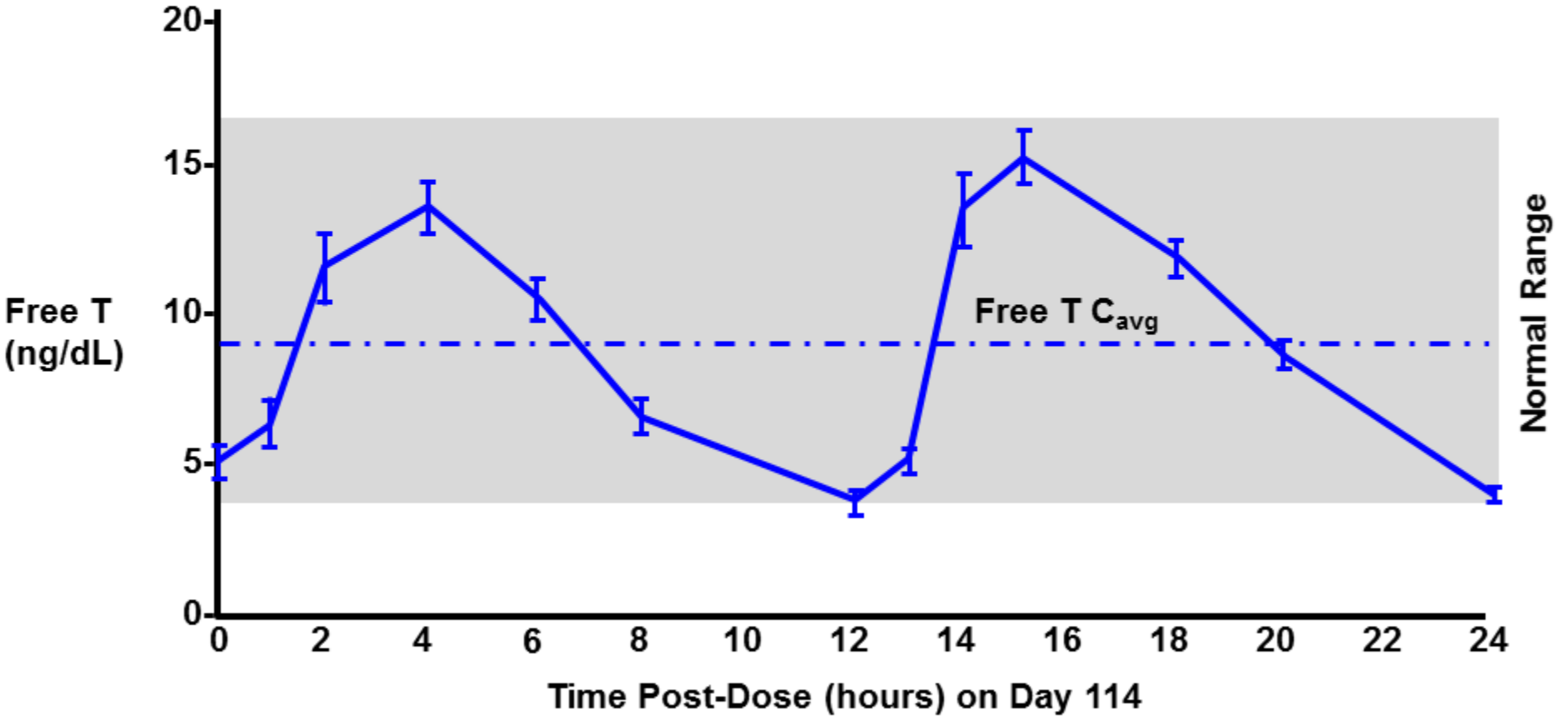
Study 12011: Serum T Profiles of Patients with Day 114 C_{max} values > 2500 ng/dL



Study 12011: Intra-Patient Variability

- C_{avg} within patient = 23%
- C_{max} within patient = 29%

Study 12011: Mean (±SEM) Free T on Day 114



Study 12011: Responses[a] Relative to Median Baseline[b] T (243.5 ng/dL) in Efficacy Population (N=116)

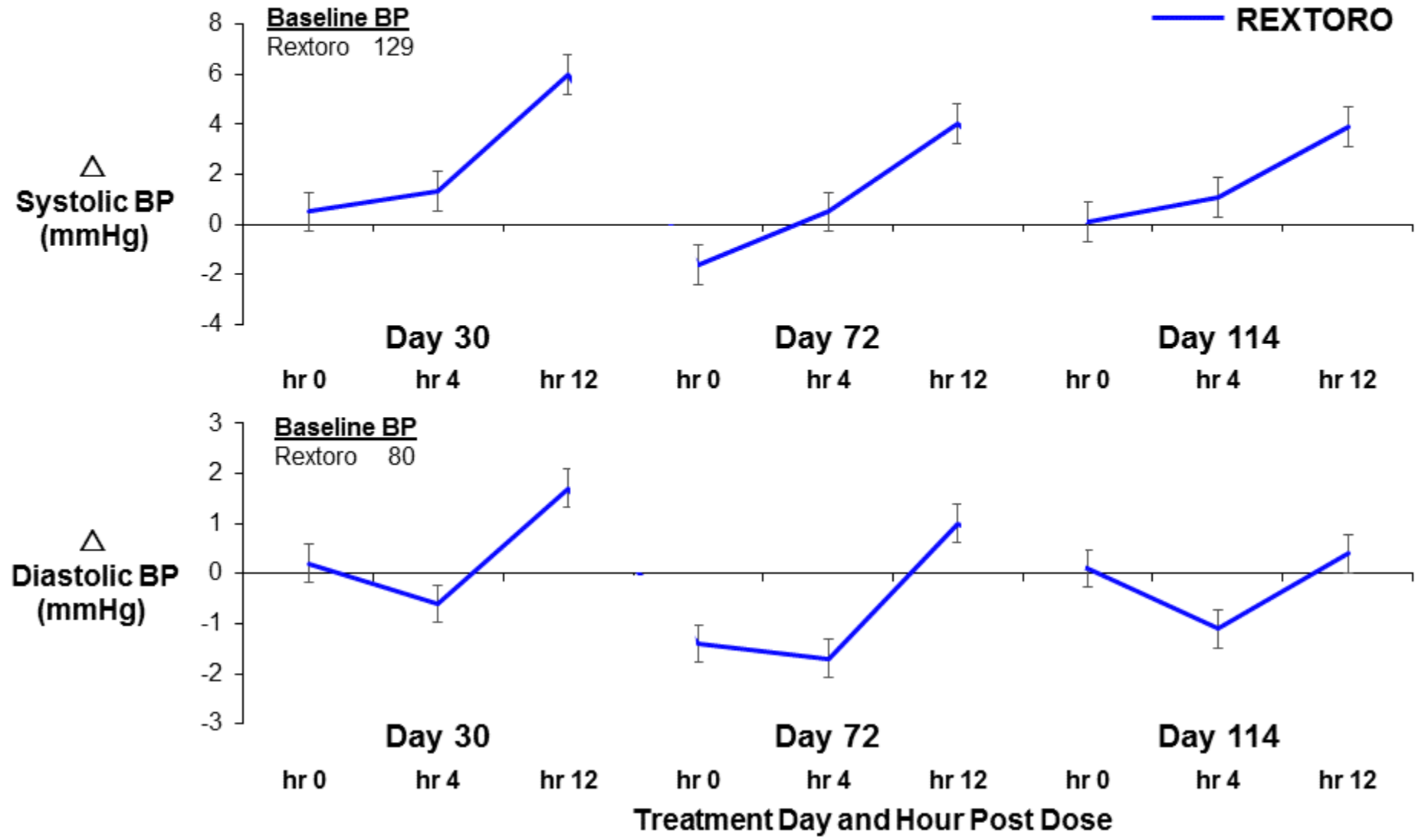
Baseline T < Median		Baseline T ≥ Median	
N	Responders	N	Responders
57	42 (73.7%)	59	45 (76.3%)

[a] Response refers to values within the Normal Range, 300 – 1000 ng/dL, inclusive.
[b] Baseline is the average of two T readings at Day 0.

Studies 09007 and 12011: Disposition

N (%) of Patients	Study 12011	Study 09007	
	REXTORO	REXTORO	AndroGel
Patients Enrolled/ Randomized	148	162	163
ITT Population	NA	162 (100%)	163 (100%)
Safety Population	144 (97.3%)	161 (99.4%)	160 (98.2%)
PK Population	133 (89.9%)	158 (97.5%)	157 (96.3%)
Efficacy Population	116 (78.4%)	146 (90.1%)	149 (91.4%)
Patients Who completed Study	117 (81.3%)	129 (79.6%)	133 (81.6%)
Patients Who Discontinued Study	27 (18.8%)	33 (20.4%)	30 (18.4%)
Adverse event	3 (2.1%)	7 (4.3%)	4 (2.5%)
Lost to follow-up	5 (3.5%)	7 (4.3%)	5 (3.1%)
Noncompliance with study drug	2 (1.4%)	3 (1.9%)	0
Protocol violation	1 (0.7%)	0	1 (0.6%)
Withdrawal of consent	8 (5.6%)	12 (7.4%)	15 (9.2%)
Hematocrit of >54%	3 (2.1%)	2 (1.2%)	0
Other	5 (3.5%)	2 (1.2%)	5 (3.1%)

Study 12011: Mean Blood Pressure (SE) Change from Baseline



Study 09007: Mean Blood Pressure (SE) Change from Baseline